UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,071	01/09/2006	Zeev Smilansky	2488.016	2101

23405 7590 05/11/2009

HESLIN ROTHENBERG FARLEY & MESITI PC
5 COLUMBIA CIRCLE
ALBANY, NY 12203

EXAMINER	
BORIN, MICHAEL L	
ART UNIT	PAPER NUMBER
1631	
MAIL DATE	DELIVERY MODE
05/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,071	SMILANSKY, ZEEV	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/19/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86,87,89-100 and 102-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86,87,89-100, 102-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Amendment filed 11/19/2008 is acknowledged. Claims 88, 101 are canceled. Claim 108 is added. Claims 86,87,89-100, 102-108 are pending.

Applicant's arguments have been fully and were deemed to be persuasive-in-part. Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Priority

2. Please disregard this section inadvertently added in the preceding Office action. This application is a national stage entry of PCT/IL/03/01011 which claims benefit of 60/429532 filed 11/29/2002.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 86,87,89-100, 102-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 86 is amended to limit the claims to use of a marker which has two labels each of which is covalently bound to different ribosome locations/components. Specification does teach that a marker may have two labels (e.g., paragraph [0026] of PreGrant publication), and more than one photo active component (paragraph [0040]); the referenced sections do not disclose that for such a marker comprising two labels both labels are bound to a target ribosome component by a covalent bond (the limitation that applicant emphasizes as a distinction over prior art). Further, specification does teach use of two labels to measure a fluorescence energy transfer – see paragraphs [0047],[0057], [0184], for example; however said sections do not disclose that such two labels used for FRET measurement are parts of the same marker.

More specifically, with respect to claims 95-97, specification does not teach markers having two labels covalently bound to two different ribosomal fragment/components as addressed in the claims. Furthermore, even though specification alleges that "at least one of the ribosome and the tRNA features a marker" (which, presumably means the same marker? – see rejection under 112, second paragraph below) there is sufficient description in specification of markers covalently bound to both tRNA and a ribosome protein (in the particular examples, paragraphs [0204]-[0224] the markers seem to be clearly different).

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 86,87,89-100, 102-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. . Claim 86 is amended to limit the claims to use of a marker which has two labels each of which is covalently bound to different ribosome locations/components. It is not clear whether the same marker is bound covalently to both a ribosome. Specification, in paragraph [0075] teaches that "at least one of the ribosome and the tRNA features a marker"; however, it is not clear whether the same marker is meant (in the particular examples, paragraphs [0204]-[0224] the markers seem to be clearly different). Please clarify via clearer claim language.

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 86,87,89-94,98,100,108 are rejected under 35 U.S.C. 102(b) as anticipated by Rothschild et al (US patent 6210941)

The instant claims are drawn to method for monitoring protein synthesis comprising

- providing a system comprising a marker detectable through detection of electromagnetic radiation, the marker comprising
  - a first label covalentlv bound to at least one ribosome or a fragment thereof, and
  - a second label covalently bound to at least one element selected from the group consisting of a different location of the ribosome or fragment thereof
- detecting electromagnetic radiation signals emitted from the system in response to protein synthesis activity, and analyzing radiation to identify protein synthesis

Rothschild et al teach method for monitoring protein synthesis comprising providing a marker that binds to tRNA which then transfers it to an amino acid of a nascent protein. Note that a part of a nascent protein is considered to be "a fragment of ribosome"[1].

[1] The phrase : "tRNA and/or amino acids and/or another part of the ribosome" in paragraph [0029] of preGrant publication is understood as demonstrating that "a part of a ribosome" encompasses both tRNA s and amino acids.

Further, Rotschild teaches that nascent proteins can be multiply labeled, which reads on use of two labels (or markers). See col. 22. Furthermore, protein synthesis can be monitored based on energy transfer from one marker to another. See col. 18, second paragraph. Rotschild teaches detecting electromagnetic radiation signals emitted from the system in response to protein synthesis activity. Col. 5, lines 26-40; col. 21-22, claims 1-25.

With respect to claim 87, the system can be cell- or in vitro translation system. See Abstract, col. 7, bottom.

With respect to claims 89-92, the marker can be fluorescent. See col. 12, for example.

With respect to claims 91-93, in addition to measuring fluorescent signal, protein synthesis can be monitored based on FRET energy transfer from one marker to another. See col. 18, second paragraph.

With respect to the new claim 108, ribosome may be a live cell – see col. 10, line 38.

Response to arguments

Applicant argues that Rotschild does not teach that labels are covalently bound, and describes interaction between tRNAs and ribosomes as being through Watson-Crick base pairs. This is not what is being meant by the rejection. The covalent binding refers to binding to amino acids of the nascent proteins. The amino acids, in turn, despite their elimination from claim language as a part of the marker, are addressed as "a part of a ribosome".

Further, applicant argues that Rotschild does not address labels becoming covalently bound upon addition to a protein translation. In response, there is no claim language requiring that labels become covalently bound upon addition to a protein translation.

7. The claims are amended to specify that the marker used to detect radiation signal comprises two labels, covalently bound to a ribosome or a fragment thereof, and to a different location of the ribosome or fragment thereof, or tRNA, respectively. Consequently, the following new rejection is applied.

Claims 86,87,89-94,98,100,108 are rejected under 35 U.S.C.103(a) as unpatentable over Odom (Biochemistry, 1990 Dec 4; 29(48):10734), and Rotschild ((US patent 6210941)) taken together with Weiss (Science, 1999, 283, 1676-1683),and Ha (Single Molecules, 2(4), pp. 283 - 284, 5 Dec 2001)

References of Odom and Rotschild teach monitoring of protein synthesis in ribosomes by monitoring fluorescence resonance transfer between two labels covalently attached to different parts or components of ribosomes .

In Odom et al., different pairs of probes were used with the energy donor attached to various sites on $tRNA^{Phe}$ and the acceptor probe on S21 or L1. Coumarin probes were covalently attached to the 5'-terminal phosphate and to s4U8 of $tRNA^{Phe}$. See p. 10739 and Table 1. The results presented in Table I indicate that the 5'-end and center region of the tRNA move toward S21 and L1 as a result of peptide transfer

to the incoming aminoacyl-tRNA. p. 10739, right column. As the FRET measurement indicate movement of a particular tRNA in the course of peptide synthesis, this is interpreted by the Examiner as indication that the results of FRET are indicative of a particular protein being synthesized.

Rothschild et al, addressed above, teach method for monitoring protein synthesis wherein a nascent protein can be multiply labeled, and protein synthesis can be monitored based on energy transfer from one marker to another. See col. 18, second paragraph, col. 22. Rotschild teaches detecting electromagnetic radiation signals emitted from the system in response to protein synthesis activity. Col. 5, lines 26-40; col. 21-22, claims 1-25.

The references, while teaching use of two labels do not teach that such two labels would be a part of the same "marker" molecule.

References of Weiss and Ha are cited to demonstrate use of single molecules having two labels for fluorescence resonance transfer studies of biological objects, such as cells. Thus, Weiss reviews use of fluorescence spectroscopy of single biomolecules having two labels and emphasizes effectiveness of use of such molecules in fluorescence energy transfer studies. p. 1677, left column, Fig. 1. In particular, the reference suggests use of such technique for monitoring movements and forces during transcription by laser tweezers and FRET in ribosomes (Fig. 6D).

Ha et al also teach uses fluorescence spectroscopy of single biomolecules having two labels and emphasizes that single-molecule FRET (smFRET) overcomes

difficulties of traditional FRET and allows to probe structural changes of biological molecules during biological events in real time and is sensitive to the internal motion or arrangement of host biological molecules. See Abstract.

Thus, it would have been prima facie obvious to one skilled in the art to be motivated to use a single "marker" having two labels which would be capable of binding to ribosome components/fragments of interest to be able to reflect the process of protein synthesis in ribosomes.

With respect to dependent claims 87,89-100, 102-108 if there are any differences between Applicant's claimed method and that of the prior art, the differences would be appear minor in nature. Although the prior art do not teach the various combinations of signal acquisition and analysis as claimed, the nature of the problem to be solved – monitoring protein synthesis in ribosomes - would lead inventors to look at references relating to possible factors known to affect detection and identification of fluorescent signals of labeled ribosome components. Based on particular situation, it would be conventional and within the skill of the art to select and/or determine such result-oriented variables as appropriate labeling sites (such as particular ribosome proteins addressed both in Odom and instant claims 96,97), conditions for signal measurement and acquisition (e.g., single *vs.* plural ribosomes, measuring after preliminary irradiation, using FRET conditions, etc), as well as signal analysis (e.g., recording signal type and comparing to database information, finding matching database information, etc). One

of ordinary skill in the art would have been motivated to combine all known factors with no change in their respective functions, and the combination would have yielded nothing more than predictable results of more comprehensive monitoring of protein synthesis.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./
Primary Examiner, Art Unit 1631